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Invited review

Paradigm shifts in understanding equine laminitis

J.C. Patterson-Kane[a], N.P. Karikoski[b], C.M. McGowan[c,*]

[a] Flagship Biosciences, 7575 W 103rd Ave #102, Westminster,CO 80021, USA
[b] Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, University of Helsinki, Viikintie49, FIN-00014 Helsinki, Finland
[c] Institutes of Veterinary Science and Ageing and Chronic Disease, Faculty of Health and Life Sciences, University of Liverpool, Leahurst CH64 7TE, UK

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ABSTRACT

Laminitis, one of the most debilitating conditions of all equids, is now known to be the result of several systemic disease entities. This finding, together with other recent developments in the field of laminitis research, have provoked a rethink of our clinical and research strategies for this condition. First, laminitis is now considered to be a clinical syndrome associated with systemic disease (endocrine disease, sepsis or systemic inflammatory response syndrome, SIRS) or altered weight bearing rather than being a discrete disease entity. Next, laminitis associated with endocrine disease (endocrinopathic laminitis) is now believed to be the predominant form in animals presenting (primarily) for lameness. Third, the designation of laminitis as a primary and severe basement membrane pathology now requires revision. Instead, current data now proposes a variable subclinical phase associated with gross changes in the hoof capsule, with stretching and elongation of the lamellar cells an early and key event in the pathophysiology. These findings have fuelled new mechanistic hypotheses and research directions that will be discussed, together with their implications for future clinical management.

Introduction

Laminitis has long been recognised as a painful condition of the hoof that causes lameness in horses (Heymering, 2010), with modern studies of the condition that can be traced back to a doctoral thesis published in the late forties (Obel, 1948). Laminitis can have debilitating long-term effects as a recurrent or chronic condition and, at worst, necessitates euthanasia of an animal in considerable pain (Hunt, 1993). At clinical presentation, we typically see lameness involving one or multiple hooves, stiffness, weight shifting, a typical 'saw horse' stance and reluctance to move, increased digital arterial pulses and sensitivity to hoof tester pressure applied at the toe of the affected digit(s) (Dyson, 2011). Many horses also present with gross hoof wall alterations that include divergent rings, increased cap horn or a wider/separated white line, and flat or convex soles (Pollitt, 2004; Collins et al., 2010; Karikoski et al., 2015) (Fig. 1).

Historically, 'classical laminitis' was linked with severe conditions associated with sepsis or systemic inflammatory response syndrome (SIRS), with deliberate starch overload or with the induction of metritis used to create experimental models (Obel, 1948). Conversely, supporting limb laminitis can result from any unilateral, painful lameness with prolonged abnormal weight bearing (Baxter and Morrison, 2009; van Eps et al., 2010; Virgin et al., 2011). The 1980s saw publication of the first hypotheses to link endocrine disease and laminitis, termed 'endocrinopathic laminitis' (Coffman and Colles, 1983; Jeffcott et al., 1986), with resistance to insulin or its abnormal regulation being a common association, especially in pony breeds.

Until relatively recently, research continued to focus on laminitis provoked by inflammation. It took a ground breaking study of a single herd of mixed Welsh and Dartmoor breed ponies, some with previous laminitis, to reveal the differences between these and 'laminitis-naive animals' (Treiber et al., 2006). Critically, these differences included higher basal insulin concentrations, plasma triglycerides, and body condition scores (Treiber et al., 2006). The five-fold increase in basal insulin concentration that accompanied the redevelopment of laminitis in a subset of ponies ($n = 13$) grazed on lush pasture was a particularly provocative finding (Treiber et al., 2006). Contemporaneously, an independent group successfully developed an experimental model of hyperinsulinaemic laminitis (Asplin et al., 2007) based on clinical observations made with horses with pituitary pars intermedia dysfunction (PPID) or other endocrine diseases (now termed equine metabolic syndrome, EMS). The high frequency of horses demonstrating (marked) hyperinsulinaemia when affected with endocrine disease was already known, together with the poorer prognosis (survival over 2 years) that accompanies presentation

* Corresponding author.
E-mail address: cmcgowan@liverpool.ac.uk (C.M. McGowan).

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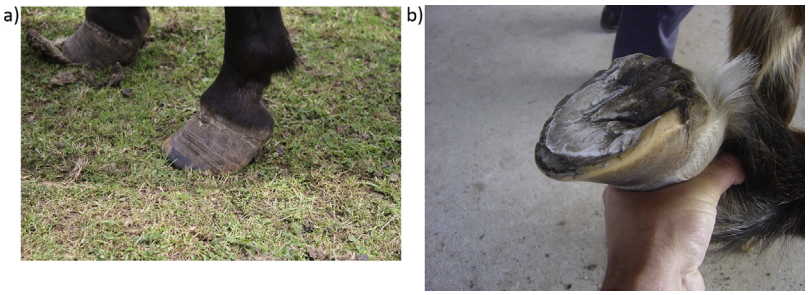

Fig. 1. (a) Divergent rings on the outer hoof wall of a pony without current lameness. (b) Solar hoof surface of a pony showing a convex or 'dropped' sole and a widened white line.

with hyperinsulinaemia (>188 μIU/mL) vs. normal or moderately increased levels of basal serum insulin (<62 μIU/mL) (McGowan et al., 2004).

More recently, studies of spontaneous endocrinopathic laminitis and hyperinsulinaemic models have markedly changed our perception of laminitis, which now warrants a re-evaluation of its clinical management and future research directions.

Paradigm shift 1: Laminitis is a clinical syndrome

Laminitis is now thought to be a clinical syndrome (rather than a discrete disease) that results from several systemic disease entities or, less frequently (as above), in the supporting limb of a lame horse (Baxter and Morrison, 2009; van Eps et al., 2010; Virgin et al., 2011; Wylie et al., 2015). Since 1948, laminitis had been considered to be a disease entity, albeit with obscure cause(s) that could be studied in the context of SIRS induced with starch or oligofructose, collectively termed carbohydrate overload models (Obel, 1948; Garner et al., 1975; Galey et al., 1991; van Eps and Pollitt, 2009). Despite recognition of the association between endocrine disease and laminitis, this connection was largely ignored. It was not until 'endocrinopathic' laminitis was unequivocally induced in a hyperinsulinaemia model that it became clear that laminitis could be provoked by multiple stimuli. Specifically, laminitis was induced in 5/5 previously healthy, young, and lean ponies following exposure to prolonged hyperinsulinaemia while maintaining euglycaemia (Asplin et al., 2007). Repetition in normal Standardbred horses yielded similar results (de Laat et al., 2010), while mild hyperglycaemia (mean ± standard error, SE, glucose 10.7 ± 0.78 mmol/L) and endogenous hyperinsulinaemia (mean ± SE insulin 208 ± 26.1 μIU/mL) induced lamellar lesions, but not a painful condition (de Laat et al., 2012).

This simple but important paradigm shift had several implications, the main one being that an accurate diagnosis of the associated systemic disease (or abnormal weight bearing) would be pivotal for laminitis management, prognosis and the prevention of recurrence. Additionally, the recognition of divergent causes of laminitis and associated risk factors (Table 1) could now improve the design of research studies that had, hitherto, proven to be inconclusive (Wylie et al., 2012).

Paradigm shift 2: Endocrinopathic laminitis predominates in animals presenting for lameness

Endocrinopathic laminitis is now recognised as the most common form of naturally occurring laminitis in horses and ponies presenting primarily with lameness in developed countries, including the USA and Europe (Donaldson et al., 2004; Karikoski et al., 2011). An earlier misconception that laminitis was predominantly associated with sepsis or SIRS arose from its prevalence in equids treated at veterinary referral hospitals, where laminitis research is concentrated (Parsons et al., 2007). This misperception was highlighted by a large epidemiological study in the USA (USDA, 2000), which showed that grain overload, retained placenta, colic or diarrhoea accounted for only 12% of owner-reported cases of laminitis; the remainder were associated with dietary problems or obesity, or were of unknown cause. Subsequent, more convincing studies from the USA and Europe

Table 1
Comparison of key signalment and clinical findings in horses ($n = 73$) developing laminitis during hospitalisation (Parsons et al., 2007) compared to those ($n = 36$) presenting with lameness due to laminitis as the primary problem (Karikoski et al., 2011).

Factor	Hospitalised horses (Parsons et al., 2007)	Primary laminitis (Karikoski et al., 2011)
Mean age	5.8 years	15 years Laminitic horses significantly older than hospital controls (9 years; $P < 0.001$)
Breeds	82.5% light breeds (Thoroughbred, Standardbred, Quarterhorse and Arabian)	86% pony, coldblood or warmblood Ponies were significantly overrepresented compared to hospital controls ($P = 0.002$)
Endotoxaemia (SIRS)[a]	Present, and significantly associated with the risk of development of laminitis on multivariable analysis (odds ratio 5, 95% confidence interval 1.37-18.19)	Not present[b]
Other indicators of illness	Yes, on univariable analysis	None
Phenotypic indicators of equine metabolic syndrome/diagnosis of pituitary pars intermedia dysfunction (PPID)	Not recorded	58%/34%
Hyperinsulinaemia	Not recorded	97%
Evidence of previous laminitis	Not recorded	86%

[a] Endotoxaemia, now termed systemic inflammatory response syndrome (SIRS), was diagnosed on the basis of clinical signs, such as hyperaemic mucous membranes and hyperaemic perialveolar gingiva, and supportive laboratory findings, such as neutropaenia and toxic changes in neutrophils (Parsons et al., 2007).
[b] Clinical evidence of SIRS was an exclusion criterion for the study (Karikoski et al., 2011).